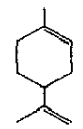
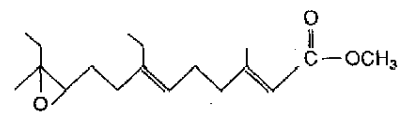
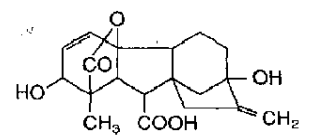
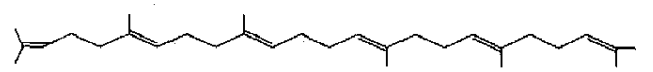
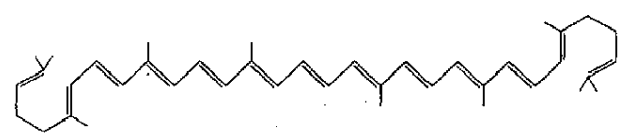
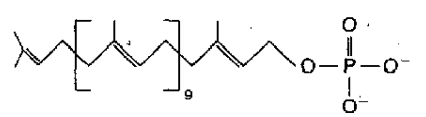
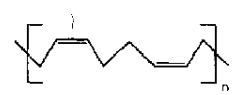
CLASS	EXAMPLE	FUNCTION
Monoterpenes	 **Limonene**	Responsible for the characteristic odor of lemons
Sesquiterpenes	 **Juvenile hormone I**	Controls metamorphosis in insects
Diterpenes	 **Gibberellic acid**	Plant growth hormone
Triterpenes	 **Squalene**	Cholesterol precursor
Tetraterpenes	 **Lycopene**	Tomato pigment
Polyprenols	 **Undecaprenol phosphate**	Sugar carrier for oligosaccharide synthesis
	 ***cis*-Polyisoprene**	Natural rubber

Figure 18.29
Some terpene compounds. These are representative of an enormous class of natural products.

Eicosanoids: Prostaglandins, Thromboxanes, and Leukotrienes

We turn finally to a class of lipids that are distinguished by their potent physiological properties, low levels in tissues, rapid metabolic turnover, and common metabolic origin. The most important of these compounds are the

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prostaglandins; also included are the **thromboxanes** and **leukotrienes**. Collectively, these compounds are called **eicosanoids** because of their common origin from C_{20} polyunsaturated fatty acids, the eicosaenoic acids. The most abundant of these acids in most lipids, and the dominant precursor, is arachidonic acid, which is *cis*-Δ^5,*cis*-Δ^8,*cis*-Δ^{11},*cis*-Δ^{14}-eicosatetraenoic acid. Related C_{20} trienoic and pentaenoic acids serve as minor precursors to some prostaglandins and their relatives. In addition to the compounds discussed here, the eicosaenoic acids serve as precursors to another class of compounds, the hydroxyeicosaenoic acids and hydroperoxyeicosaenoic acids. The latter compounds are metabolic precursors to the leukotrienes.

The prostaglandins and the closely related thromboxanes are derived from a common pathway; a different pathway leads from arachidonic acid to the leukotrienes. Like hormones, the eicosanoids exert specific physiological effects on target cells. However, they are distinct from most hormones in that they act locally, near their sites of synthesis, and they are catabolized extremely rapidly. Moreover, the actions of a given prostaglandin seem to vary in different tissues. The biological properties of the eicosanoids have led to great interest in their medical use and in uses of their analogs.

Some Historical Aspects

The most important early chapters in prostaglandin research were written in Sweden. In the mid-1930s Ulf von Euler discovered that lipid extracts of human semen contained active compounds that, on injection into animals, stimulated smooth muscle contraction or relaxation and affected the blood pressure. Because of their presumed origin in the prostate gland, he named these compounds *prostaglandins*. Later it was realized that these compounds are widely distributed in animal tissues. The first structural elucidations were reported in the late 1950s, under the direction of Sune Bergstrom and Bengt Samuelsson, and biosynthetic pathways were described in the mid-1960s, in Sweden and in the Netherlands.

The biological properties of the prostaglandins attracted intense interest in the pharmaceutical industry, but initial progress was limited by the low availabilities of these compounds. Interest reached a peak in 1971 with the discovery that aspirin inhibits one of the enzymes in prostaglandin biosynthesis. This inhibition is now known as the major site of action of aspirin and other nonsteroidal anti-inflammatory drugs. Later in the 1970s the thromboxanes and leukotrienes were discovered.

Structure

The first two prostaglandins to be isolated were called prostaglandins E and F, respectively, because of their preferential solubility in ether (E) or in phosphate buffer (F for *fosfat*, the Swedish word). We now denote these compounds by PGE and PGF, respectively; all other prostaglandins are denoted by a letter, for instance, PGA and PGH. Each prostaglandin has a cyclopentane ring and two side chains, with a carboxyl group in one side chain. A subscript numeral denotes the number of double bonds in the two chains. The most abundant prostaglandins, those synthesized from arachidonic acid, contain two double bonds; thus, PGE_2 would be the prostaglandin E derived from arachidonic acid. Finally, a subscript α indicates that the hydroxyl group at C-9 is on the same side of the ring as the carboxyl group. Structures of the most common prostaglandins are shown in Figure 18.30, along with that of thromboxane A_2 (TxA_2). TxA_2 is the only known naturally occurring thromboxane; it was originally isolated from thrombocytes,

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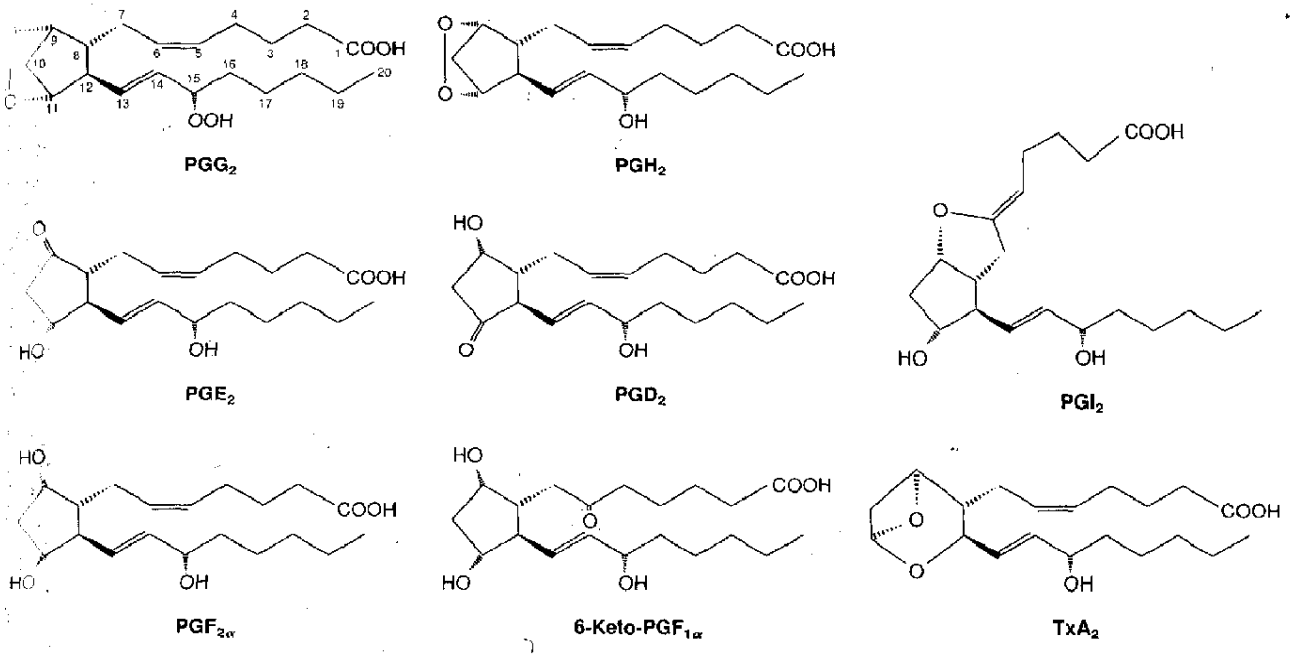

Figure 18.30
Structures of the major prostaglandins and thromboxane derived from arachidonic acid. Numbering of carbons begins with the carboxyl group.

or blood platelets, as a compound that stimulated platelet aggregation, an early step in blood clotting. Note its structural resemblance to PGE_2, except for the cyclic ether ring. Another thromboxane, TxB_2, is a hydrolysis product of TxA_2.

Biosynthesis and Catabolism

Here we discuss only the biosynthesis of the 2-series of prostaglandins; the 1- and 3-prostaglandins are synthesized identically, from related C_{20} fatty acids. We can consider the biosynthetic pathways, which occur in endoplasmic reticulum, as three distinct stages: (1) release of arachidonic acid from membrane phospholipids; (2) oxygenation of arachidonate to yield PGH, a prostaglandin endoperoxide that serves as precursor to other prostaglandins; and (3) depending on the enzymes present in a cell, the conversion of PGH to other prostaglandins or to TxA_2. The biosynthetic pathways are summarized in Figure 18.31.

The release of arachidonic acid in stage 1 occurs as a result of tissue-specific stimuli by hormones such as bradykinin or epinephrine, or proteases such as thrombin. Pathological release can occur if membranes are perturbed; for example, the inflammation caused by bee stings is probably due to arachidonate release stimulated by the venom protein **melittin.** Release evidently involves the action of a specific phospholipase A_2 on phosphatidylcholine or phosphatidylethanolamine, yielding arachidonate, and the action of a phospholipase C on phosphatidylinositol, yielding a diacylglycerol, which in turn undergoes cleavage to give free arachidonate.

Free arachidonate is acted on, in stage 2, by **PGH synthase,** a bifunctional enzyme with two activities in a single heme-containing polypeptide chain. The first, a **cyclooxygenase,** introduces two molecules of O_2, one to form the ring and one to form a hydroperoxy group at C-15. The second

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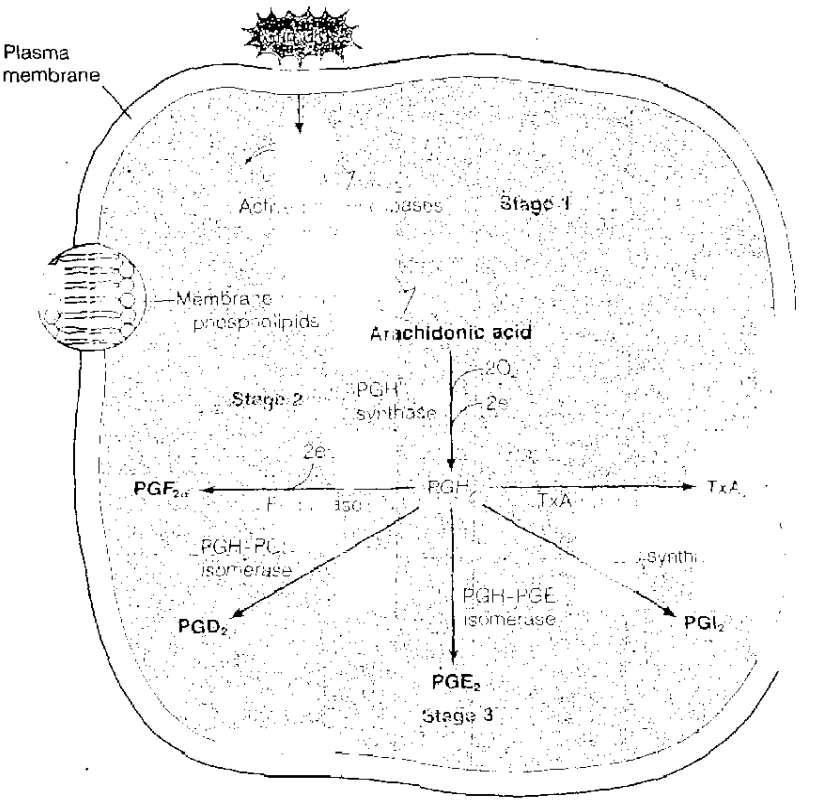
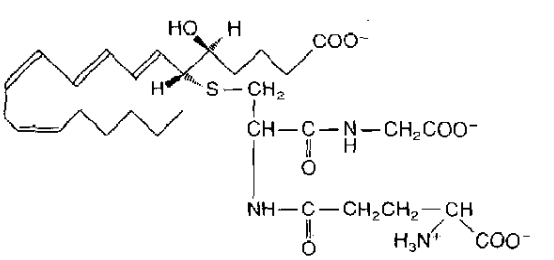


Figure 18.31
Summary of biosynthetic routes to the 2-series of prostaglandins (the most abundant group) and thromboxane A_2.

activity involves a two-electron reduction of the peroxide, to give PGH_2, with a hydroxyl group at C-15, as shown in Figure 18.32. The cyclooxygenase activity is the target for aspirin (acetylsalicylic acid), which acetylates a serine residue critical for activity and is in turn converted to salicylic acid.

In stage 3 a series of specific enzymes converts PGH_2 to other prostaglandins and to thromboxane A_2.

Another pathway leads from arachidonate to the leukotrienes. Leukotriene C was originally discovered in the class of white blood cells called polymorphonuclear leukocytes. It is a potent muscle contractant that is thought to be involved in the pathogenesis of asthma, through constriction of the small airways in the lung. Leukotrienes are formed from the initial attack on arachidonate of a **lipoxygenase**, which adds O_2 to C-5. A dehydration to give the epoxide coupled with isomerization of double bonds, followed by transfer of the thiol group of glutathione to one of the epoxide carbons, yields leukotriene C.



Leukotriene C

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ubsequent modifications of the peptide chain yield related compounds, eukotrienes D and E.

All of the eicosanoids are metabolized extremely rapidly, with most iling to survive a single pass through the circulatory system. The lung is a jor site of prostaglandin catabolism. The many catabolic pathways all em to start with conversion to 15-keto-13,14-dihydro derivatives.

Biological Actions

As noted earlier, prostaglandins and their relatives can be considered as locally acting hormones. Evidently they act through binding to specific cellular receptors. We know relatively little about their subsequent effects at the molecular level, though there clearly are interactions with cyclic nucleotide metabolism. PGE stimulates adenylate cyclase in some cells, and PGF_2 has been reported to elevate levels of **cyclic guanosine monophosphate** in target cells.

Although little is known so far about molecular actions of the eicosanoids, knowledge of their physiology is being applied in useful ways. Since prostaglandin release is involved in the uterine muscle contraction that occurs in labor, PGF_2 is being used when it is necessary to induce labor in mothers at term. PGF_2 and PGE_2 are used as well to induce abortion in the second trimester, or to induce delivery in case of the death of a fetus. Prostaglandin derivatives are used in animal husbandry, to bring a group of female animals into heat simultaneously. PGI_2 is used to reduce the risk of blood clotting during cardiopulmonary bypass operations. PGE_1, a vasodilator, is being tested against various circulatory disorders, and forms of PGE, which also inhibit gastric secretion, are being used in treatment of stomach ulcers. Efforts in the pharmaceutical industry are devoted to developing longer-lived prostaglandin analogs.

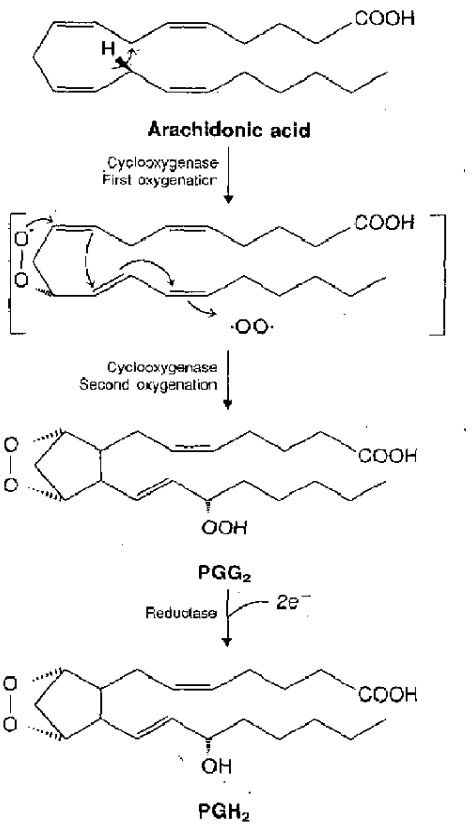

Figure 18.32
Probable mechanism for the cyclooxygenation of arachidonic acid by PGH synthase.

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plays an important role the anticonvulsant therapy with mi-lacemide (Benedetti and Dostert, 1994).

Diamine oxidase is a cytosolic, copper-containing, pyridoxal phosphate-dependent enzyme present in liver, kidney, intestine, and placenta. Its preferred substrates include histamine and simple alkyl diamines with a chain length of 4 (putrescine) or 5 (cadaverine) carbon atoms. Diamines with carbon chains longer than 9 are not substrates for DAO, although they can be oxidized by MAO. DAO or a similar enzyme is present in cardiovascular tissue and appears to be responsible for the cardiotoxic effects of allylamine, which is converted by oxidative deamination to acrolein.

Aromatization. The conversion of MPTP to MPP^+ (Fig. 6-20) is an example of a xenobiotic whose oxidation involves the introduction of multiple double bonds to achieve some semblance of aromaticity (in this case, formation of a pyridinium ion). Aromatization of xenobiotics is an unusual reaction, but some examples have been documented. A mitochondrial enzyme in guinea pig and rabbit liver can oxidize several cyclohexane derivatives to the corresponding aromatic hydrocarbon, as shown in Fig. 6-21 for the aromatization of cyclohexane carboxylic acid (hexahydrobenzoic acid) to benzoic acid. Mitochondria from rat liver are less active, and those from cat, mouse, dog, monkey, and human are completely inactive. The reaction requires magnesium, coenzyme A, oxygen, and ATP. The first step appears to be the formation of hexahydrobenzoyl-CoA, which is then dehydrogenated to the aromatic product. Glycine stimulates the reaction, probably by removing benzoic acid through conjugation to form hippuric acid (a phase II reaction). The conversion of androgens to estrogens involves aromatization of the A-ring of the steroid nucleus. This reaction is catalyzed by CYP19, one of the cytochrome P450 enzymes involved in steroidogenesis.

Peroxidase-Dependent Cooxidation. The oxidative biotransformation of xenobiotics generally requires the reduced pyridine nucleotide cofactors, NADPH and NADH. An exception is xenobiotic biotransformation by peroxidases, which couple the reduction of hydrogen peroxide and lipid hydroperoxides to the oxidation of other substrates, a process known as *cooxidation* (Eling et al., 1990). Several different peroxidases catalyze the biotransformation of xenobiotics, and these enzymes occur in a variety of tissues and cell types. For example, kidney medulla, platelets, vascular endothelial cells, the gastrointestinal tract, brain, lung, and urinary bladder epithelium contain prostaglandin H synthase (PHS); mammary gland epithelium contains lactoperoxidase, and leukocytes contain myeloperoxidase. PHS is the most extensively studied peroxidase in-

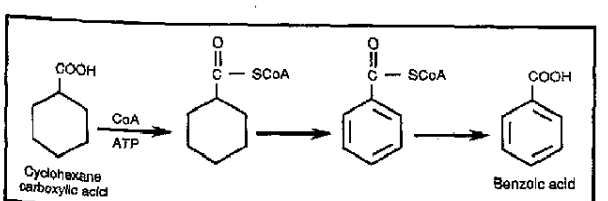

Figure 6–21. Aromatization of cyclohexane carboxylic acid, a reaction catalyzed by rabbit and guinea pig liver mitochondria.

volved in the xenobiotic biotransformation. This enzyme possesses two catalytic activities: a *cyclooxygenase* that converts arachidonic acid to the cyclic endoperoxide-hydroperoxide PGG_2 (which involves the addition of two molecules of oxygen to each molecule of arachidonic acid), and a *peroxidase* that converts the hydroperoxide to the corresponding alcohol PGH_2 (which can be accompanied by the oxidation of xenobiotics). The conversion of arachidonic acid to PGH_2, which is subsequently converted to a variety of eicosanoids (prostaglandins, thromboxane, and prostacyclin), is shown in Fig. 6-22. PHS and other peroxidases play an important role in the activation of xenobiotics to toxic or tumorigenic metabolites, particularly in extrahepatic tissues that contain low levels of cytochrome P450 (Eling et al., 1990).

In certain cases, the oxidation of xenobiotics by peroxidases involves direct transfer of the peroxide oxygen to the xenobiotic, as shown in Fig. 6-22 for the conversion of substrate X to product XO. An example of this type of reaction is the PHS-catalyzed epoxidation of benzo[a]pyrene 7,8-dihydrodiol to the corresponding 9,10-epoxide (see Fig. 6-5). Although PHS can catalyze the final step (i.e., 9,10-epoxidation) in the formation of this tumorigenic metabolite of benzo[a]pyrene, it cannot catalyze the initial step (i.e., 7,8-epoxidation), which is catalyzed by cytochrome P450. The 9,10-epoxidation of benzo[a]pyrene 7,8-dihydrodiol can also be catalyzed by 15-lipoxygenase, which is present at high concentrations in human pulmonary epithelial cells, and by peroxyl radicals formed during lipid peroxidation in skin. Cytochrome P450 and peroxyl radicals formed by PHS, lipoxygenase, and/or lipid peroxidation may all play a role in activating benzo[a]pyrene to metabolites that cause lung and skin tumors. These same enzymes can also catalyze the 8,9-epoxidation of aflatoxin B_1, which is one of the most potent hepatotumorigens known. Epoxidation by cytochrome P450 is thought to be primarily responsible for the hepatotumorigenic effects of aflatoxin B_1. However, aflatoxin B_1 also causes neoplasia of rat renal papilla. This tissue has very low levels of cytochrome P450, but contains relatively high levels of PHS, which is suspected, therefore, of mediating the nephrotumorigenic effects of aflatoxin (Fig. 6-23).

The direct transfer of the peroxide oxygen from a hydroperoxide to a xenobiotic is not the only mechanism of xenobiotic oxidation by peroxidases, nor is it the most common. As shown in Fig. 6-22, xenobiotics that can serve as electron donors, such as amines and phenols, can be oxidized to free radicals during the reduction of a hydroperoxide. In this case, the hydroperoxide is still converted to the corresponding alcohol, but the peroxide oxygen is reduced to water instead of being incorporated into the xenobiotic. For each molecule of hydroperoxide reduced (which is a two-electron process), two molecules of xenobiotic can be oxidized (each by a one-electron process). Important classes of compounds that undergo one-electron oxidations by peroxidase include aromatic amines, phenols, hydroquinones and polycyclic hydrocarbons. Many of the metabolites produced are reactive electrophiles. For example, polycyclic aromatic hydrocarbons, phenols, and hydroquinones are oxidized to electrophilic quinones. Acetaminophen is similarly converted to a quinoneimine, namely *N*-acetyl-benzoquinoneimine, a cytotoxic electrophile that binds to cellular proteins, as shown in Fig. 6-24. The formation of this toxic metabolite by cytochrome P450 causes

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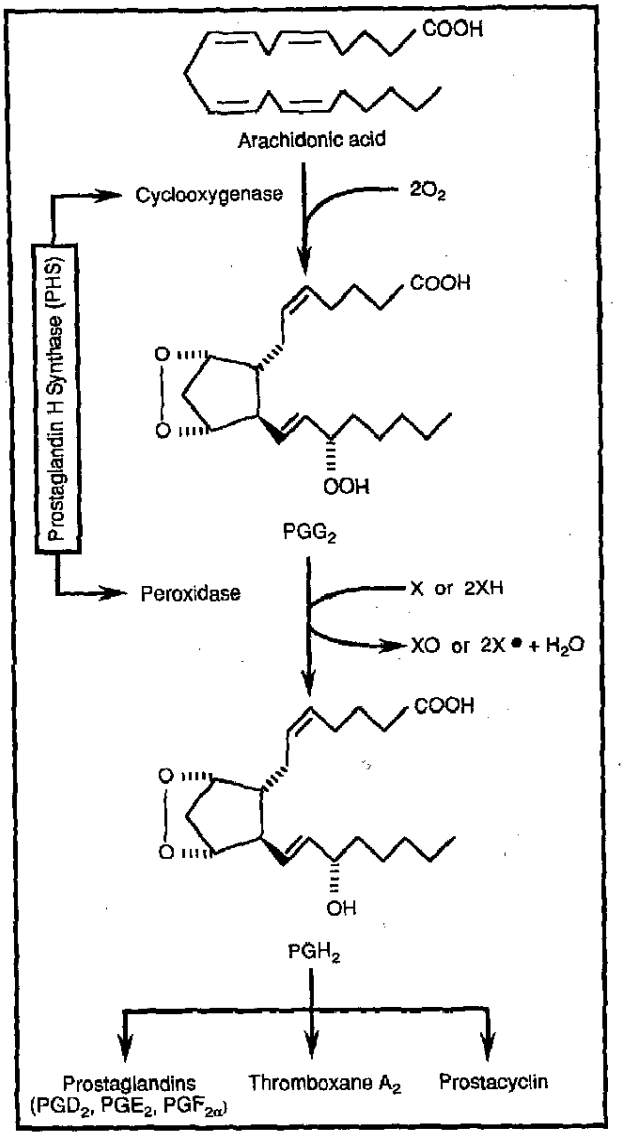

Figure 6–22. Cooxidation of xenobiotics (X) during the conversion of arachidonic acid to PGH_2 by prostaglandin H synthase.

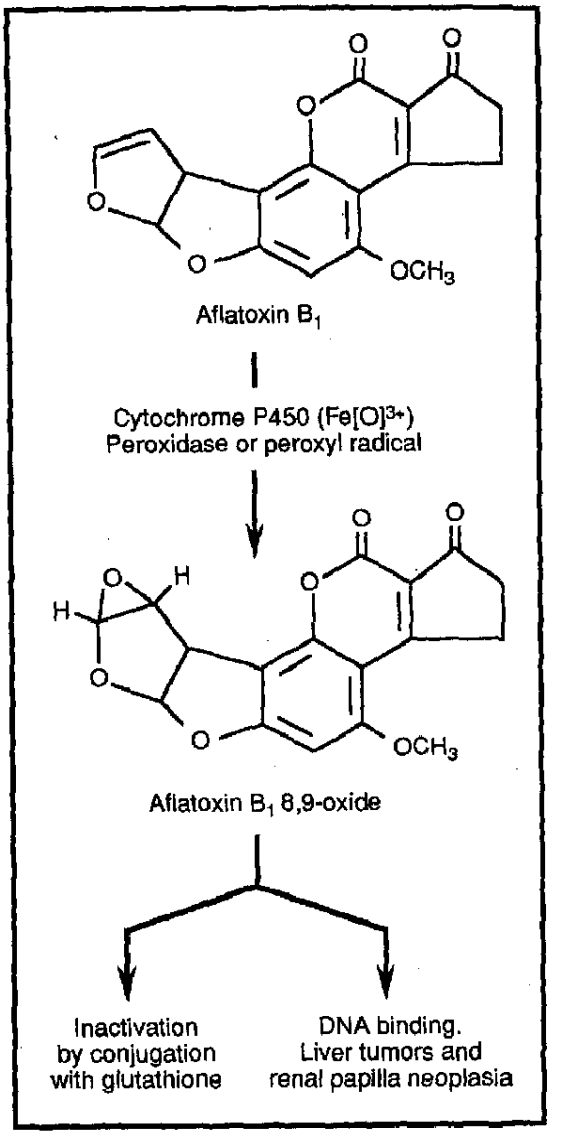

Figure 6–23. Activation of aflatoxin B_1 by cytochrome P450, leading to liver tumor formation, and peroxidases, leading to renal papilla neoplasia.

centrilobular necrosis of the liver. However, acetaminophen can also damage the kidney medulla, which contains low levels of cytochrome P450 but relatively high levels of PHS; hence, PHS may play a significant role in the nephrotoxicity of acetaminophen. The two-electron oxidation of acetaminophen to *N*-acetyl-benzoquinoneimine by PHS likely involves the formation of a one-electron oxidation product, namely *N*-acetyl-benzosemiquinoneimine radical. Formation of this semiquinoneimine radical by PHS likely contributes to the nephrotoxicity of acetaminophen and related compounds, such as phenacetin and *p*-aminophenol.

Like the kidney medulla, urinary bladder epithelium also contains low levels of cytochrome P450 but relatively high levels of PHS. Just as PHS in kidney medulla can activate aflatoxin and acetaminophen to nephrotoxic metabolites, so PHS in urinary bladder epithelium can activate certain aromatic amines, such as benzidine, 4-aminobiphenyl, and 2-aminonaphthalene, to DNA-reactive metabolites that cause bladder cancer in certain species, including humans and dogs. As illustrated in Fig. 6-25, PHS can convert aromatic amines to reactive radicals, which can undergo nitrogen-nitrogen or nitrogen-carbon coupling reactions, or they can undergo a second one-electron oxidation to reactive diimines. Binding of these reactive metabolites to DNA is presumed to be the underlying mechanism by which several aromatic amines cause bladder cancer in humans and dogs. In some cases the one-electron oxidation of an amine leads to *N*-dealkylation. For example, PHS catalyzes the *N*-demethylation of ami-

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